Invasive Pulmonary Aspergillosis-mimicking Tuberculosis

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Background. Pulmonary tuberculosis is occasionally confused with invasive pulmonary aspergillosis (IPA) in transplant recipients, since clinical suspicion and early diagnosis of pulmonary tuberculosis and IPA rely heavily on imaging modes such as computed tomography (CT). We therefore investigated IPA-mimicking tuberculosis in transplant recipients.

Methods. All adult transplant recipients who developed tuberculosis or IPA at a tertiary hospital in an intermediate tuberculosis-burden country during a 6-year period were enrolled. First, we tested whether experienced radiologists could differentiate pulmonary tuberculosis from IPA. Second, we determined which radiologic findings could help us differentiate them.

Results. During the study period, 28 transplant recipients developed pulmonary tuberculosis after transplantation, and 80 patients developed IPA after transplantation. Two experienced radiologists scored blindly 28 tuberculosis and 50 randomly selected IPA cases. The sensitivities of radiologists A and B for IPA were 78% and 68%, respectively (poor agreement, kappa value = 0.25). The sensitivities of radiologists A and B for tuberculosis were 64% and 61%, respectively (excellent agreement, kappa value = 0.77). We then compared the CT findings of the 28 patients with tuberculosis and 80 patients with IPA. Infarct-shaped consolidations and smooth bronchial wall thickening were more frequent in IPA, and mass-shaped consolidations and centrilobular nodules (<10 mm, clustered) were more frequent in tuberculosis.

Conclusions. Certain CT findings appear to be helpful in differentiating between IPA and tuberculosis. Nevertheless, the CT findings of about one-third of pulmonary tuberculosis cases in transplant recipients are very close to those of IPA.

Keywords. tuberculosis; aspergillosis; computed tomography.

Tuberculosis is a significant opportunistic infection in transplant recipients [1]. Mycobacterial culture is the gold standard for diagnosis of tuberculosis, but it takes 2–6 weeks. Therefore, clinical suspicion and early treatment of pulmonary tuberculosis in transplant recipients mostly rely on imaging modes such as chest computed tomography (CT). In general, the common CT findings of postprimary pulmonary tuberculosis such as centrilobular nodules, branching linear and nodular opacities, patchy or lobular areas of consolidation, and cavities, are helpful in distinguishing it from other pulmonary infectious diseases [2]. However, the radiologic features of pulmonary tuberculosis in immunocompromised patients can vary [3]. As a result, the CT findings of pulmonary tuberculosis in transplant recipients are occasionally confused with those of invasive pulmonary aspergillosis (IPA), which is also an important opportunistic infection in these patients [4, 5]. However, data on this issue are limited. South Korea has an incidence in 2013 of 97 cases per 100 000 Korean [6]. We therefore have a unique opportunity to compare the CT findings for pulmonary tuberculosis in transplant recipients with those of IPA in transplant recipients because the incidence of tuberculosis is so low in the United States

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(3.3 cases per 100 000 in 2013) that enough number of tuberculosis cases to perform this analysis is logistically difficult. We thus investigated IPA-mimicking tuberculosis in transplant recipients.

MATERIALS AND METHODS

Study Population

This study was performed at the Asan Medical Center, a 2700-bed tertiary care teaching hospital in Seoul, South Korea, from January 2008 to December 2013. All adult transplant recipients who developed microbiologically confirmed tuberculosis during the study period were retrospectively enrolled. The study focused on the clinical features and CT findings of IPA-mimicking tuberculosis. We therefore only included pulmonary tuberculosis and excluded extrapulmonary and miliary tuberculosis. We also excluded pulmonary tuberculosis where there was coinfection with other pathogens (Figure 1). All adult transplant recipients who developed IPA during the study period were also retrospectively enrolled and we again excluded cases with co-infections. In addition, we excluded neutropenic patients with IPA. Patients were assigned a proven or probable diagnosis of IPA according to the consensus definition of the EORTC/MSG [7] and our previous reports [8–11]. Briefly, proven IPA was identified by histologic evidence of tissue invasion, including septated, acutely branching filamentous fungi and positive culture. Probable IPA was defined as the presence of a host factor, together with a clinical factor and a mycologic factor. This retrospective study from a single tertiary center was approved by the Institutional Review Board. Informed consent was waived.

Study Design and Definitions

In the first part of the study we tested whether experienced radiologists could differentiate pulmonary tuberculosis from IPA. Two independent experienced radiologists reviewed blind 78 CT images from the 28 patients with pulmonary tuberculosis and the 50 randomly selected patients with IPA. The exact numbers of tuberculosis cases and IPA cases were unknown to the radiologists. To avoid random decisions between tuberculosis and IPA, indeterminate answers were classified as wrong diagnoses. For example, we asked the radiologists to select "TB", "indeterminate", or "IPA" as the answer for each of these 78 CT images. To evaluate their ability to diagnose tuberculosis, only answers of "TB" were classified as correct. To evaluate their ability to diagnose IPA, only answers of "IPA" as an answer was classified as correct. In the second part of the study we determined which radiologic findings were able to help differentiate pulmonary tuberculosis from IPA. The 2 independent

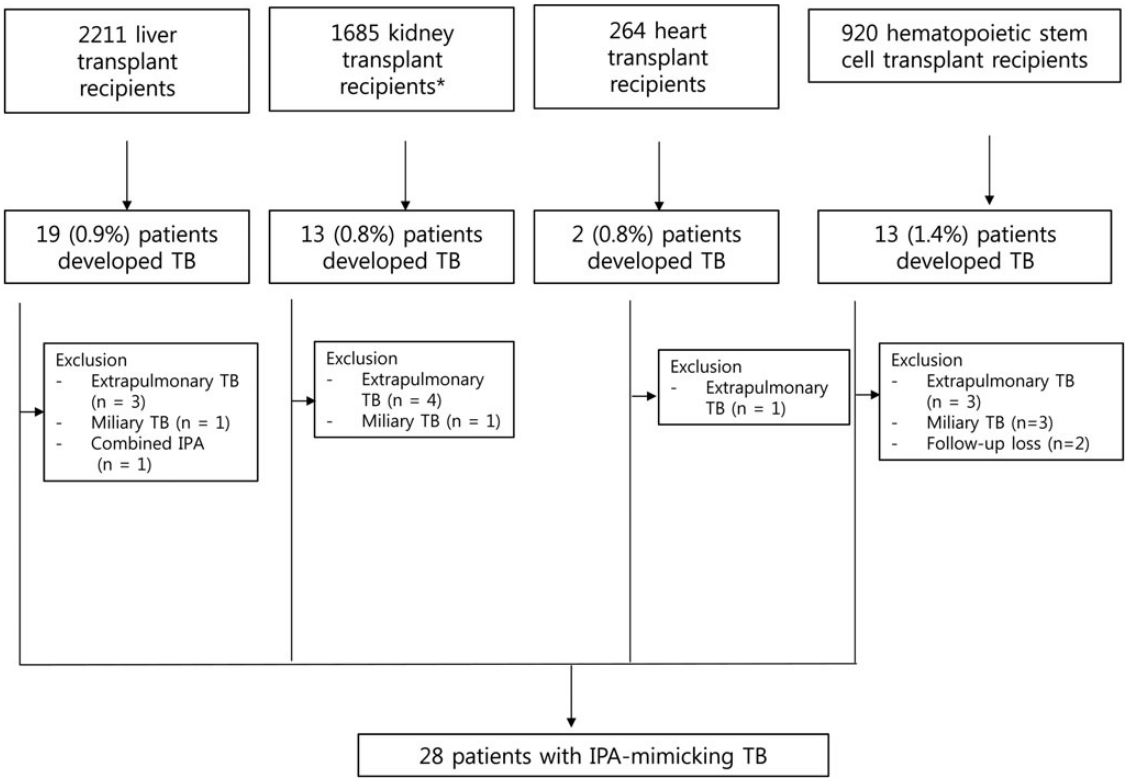

Figure 1. Flow diagram for selecting cases of pulmonary tuberculosis (TB). *The 1685 kidney transplant recipients included 1652 kidney and 33 pancreas transplant recipients. Abbreviation: IPA, invasive pulmonary aspergillosis.

radiologists reviewed the CT findings of the 28 patients with pulmonary tuberculosis and the 80 patients with IPA. The 2 radiologists were also unaware of the patients' diagnoses during the second part of the study.

The anti-tuberculosis treatments were classified as empirical or definitive, with the former being defined as receipt of anti-tuberculosis treatment with first-line drugs before a positive mycobacterial culture or a positive *M. tuberculosis* polymerase chain reaction (PCR) assay or positive acid-fast bacilli (AFB) stain was obtained and the latter being defined as receipt of standard anti-tuberculosis treatment with first-line drugs after a positive result of mycobacterial culture or a positive *M. tuberculosis* PCR assay or positive AFB stain.

CT Evaluation

The 2 independent radiologists (M. Y. K.; 18 years' experience in thoracic radiology, H. J. L.; 6 years' experience in thoracic radiology) were unaware of the patients' characteristics and clinical outcomes. Where there was disagreement the final decision was made by consensus. We reviewed the first CT image from the symptom onset. A total of 108 CT scans were obtained with (n = 18) or without (n = 90) contrast enhancement. All images were viewed on theat mediastinal (width, 450 HU; level, 50 HU) and lung window (width, 1500 HU; level, −700 HU) settings of the axial image on a picture archiving communication system.

We used a glossary of CT imaging definitions to categorize pulmonary lesions [12]. Radiological patterns of IPA were classified as angio-invasive, airway-invasive, or necrotizing pneumonia, based on previous studies [9, 13, 14]. The following radiologic patterns were considered angio-invasive: macronodules, an infarct-shaped consolidation, a halo sign, or a mass-shaped consolidation. The following radiologic pattern was considered as airway-invasive form: clusters of centrilobular nodules, a peribronchial consolidation, a ground-glass opacity, or a smooth bronchial wall thickening. The following radiologic pattern was considered as necrotizing pneumonia: air-crescent sign, a cavitary lesion, internal low attenuation, or a reverse halo sign or a bird nest sign.

An infarct-shaped consolidation was defined as triangular or dome-shaped, with the base abutting the pleura and the apex directed toward the hilum with or without a cavity. A peribronchial consolidation was defined as centered on macroscopic bronchovascular bundles or with a peribronchial distribution with or without smooth bronchial wall thickening [12]. A mass-shaped consolidation was defined as a homogeneous increase in parenchymal attenuation, with a tumor-like measurable lesion, more than 3 cm in long diameter, with or without air bronchograms.

Tree-in-bud appearance was defined as clustered 2–4-mm nodular and linear branching centrilobular opacities with a lobular or segmental distribution on CT, indicative of small–airway disease, initially used to describe the appearance of the endobronchial spread of tuberculosis [15].

Statistical Analysis

Categorical variables were compared using the χ^2 or Fisher exact test, as appropriate, and continuous variables using Student *t* test and the Mann–Whitney *U* test, as appropriate. Diagnostic performance was expressed in terms of sensitivity. Concordance between the radiologists A and B was assessed using the kappa. All tests of significance were two-tailed and a *P* value of less than .05 was considered to indicate statistical significance. Calculations were performed using the SPSS for Windows software package, version 21 K (SPSS Inc, Chicago, Illinois).

RESULTS

Study Characteristics

During the study period, 5080 transplants, namely, 2211 liver transplants (LT), 1685 kidney transplants (KT) with 33 pancreas transplants, 264 heart transplants (HT), and 920 allogeneic hematopoietic stem cell transplants (HCT) were performed. Of the transplant recipients, 47 developed tuberculosis after transplantations (925 cases per 100 000 persons), so the incidence is 10 times greater than in Korean general population (97 cases per 100 000 persons). The incidence of tuberculosis (Figure 1) showed a trend toward being higher in HCT recipients (1.4%) than solid organ transplant recipients (0.8%, $P = .09$), although this did not reach any statistical significance. Of these 47 patients, 11 had extrapulmonary tuberculosis, 5 miliary tuberculosis, 1 combined IPA, and due to inadequate follow-up 2 were excluded from the analysis. Finally the remaining 28 patients, who had pulmonary tuberculosis were analyzed. In addition, 128 patients consisting of 8 confirmed and 120 probable IPA with exclusion of 34 patients with co-infection were identified as developing IPA after transplantation during the study period, and the 80 transplant recipients having IPA with the exclusion of 48 IPA in neutropenic HCT recipients were included in the final analysis.

A comparison of the baseline clinical characteristics of the 28 tuberculosis and 80 IPA patients is shown in Table 1. Tuberculosis (median time 138 days, interquartile range [IQR] 92–289) developed later after transplantation than IPA (median time 67 days, IQR 27–192, $P = .001$), but their IQRs overlapped substantially. The median time from symptom onset to diagnosis was also longer in the tuberculosis group (26 days) than the IPA group (7 days; $P < .001$). Interestingly, serum galactomannan (GM) and bronchoalveolar larvage (BAL) fluid GM were positive in 12% and 14% of the patients with tuberculosis, respectively. The detailed demographic and clinical characteristics of these patients with tuberculosis who showed positive GM are shown in Supplementary Table 1.

Of the 80 transplant patients with IPA, none received empirical anti-tuberculosis treatment. However, of the 28 transplant patients with pulmonary tuberculosis, 15 (53%) received empiric anti-tuberculosis treatment without antifungal treatment,

Table 1. Baseline Clinical Characteristics of 28 Transplant Patients With tuberculosis and 80 Patients With IPA

	TB (n = 28)	IPA (n = 80)	*P* Value
Age, mean years ± SD	49 ± 13	50 ± 12	.85
Male gender	18 (64)	57 (71)	.49
Median time from transplantation, days (IQR)	138 (92–289)	67 (27–192)	.001
Median time from symptom onset to diagnosis, days (IQR)	26 (11–50)	7 (3–13)	<.001
Transplant type			
Liver transplant	14 (50)	48 (60)	.36
Kidney transplant	8 (29)	7 (9)	.02
Heart transplant	1 (3)	9 (11)	.45
Hematopoietic stem cell transplant	5 (18)	16 (20)	.80
LTBI screening before transplantation			
Abnormal chest radiograph	6 (21)	9 (11)	.21
Prior history of TB	1 (4)	5 (6)	>.99
Tuberculin skin test	0/9[a] (0)	0/5[a] (0)	NA
T-SPOT.*TB*	3/7[a] (43)	2/4[a] (50)	>.99
QuantiFERON-TB In-Tube	1/5[a] (20)	1/18[a] (6)	.40
LTBI treatment	1 (4)	1 (1)	.45
Diagnostic category of TB or IPA			
Confirmed	28 (100)	6 (8)	NA
Probable	NA	74 (92)	NA
Positive AFB smear from respiratory specimen	10 (36)	NA	NA
Positive serum galactomannan assay	2/17 (12)	63/80 (79)	<.001
Positive BAL galactomannan assay	1/7 (14)	26/32 (81)	.002
Median time from the symptom onset to the first CT, days (IQR)	10 (2–23)	7 (3–13)	.30
Initial CT reading			
Bacterial pneumonia	11 (39)	43 (54)	.19
Fungal pneumonia	5 (18)	31 (39)	.02
TB	11 (39)	4 (5)	<.001
Others	1 (4)	2 (3)	>.99
Inappropriate antifungal therapy	8 (29)	NA	NA
TB or IPA-related mortality	1 (4)	28 (35)	.001

Note: Data are no. (%) of patients, unless otherwise indicated.

Abbreviations: AFB, acid-fast bacilli; BAL, bronchoalveolar larvage; CT, computed tomography; IPA, invasive pulmonary aspergillosis; IQR, interquartile range; LTBI, latent tuberculosis infection; NA, not applicable; SD, standard deviation; TB, tuberculosis.

[a] No. of patients with a positive test result/number of patients tested.

Table 2. Concordance in the Scoring of 28 tuberculosis and 50 Randomly Selected IPA Cases Between the Two Radiologists

	IPA Score		
	Radiologist B		
	IPA	Not IPA	Total
Radiologist A			
IPA	29	10	39 (78)
Not IPA	5	6	11 (22)
Total	34 (68)	16 (32)	50 (100)
Kappa value = 0.25			
	TB score		
	Radiologist B		
	TB	Not TB	Total
Radiologist A			
TB	16	2	18 (64)
Not TB	1	9	10 (36)
Total	17 (61)	11 (39)	28 (100)
Kappa value = 0.77			

Note: Data are no. (%) of patients.

Abbreviations: IPA, invasive pulmonary aspergillosis; TB, tuberculosis.

8 (29%) received empirical antifungal treatment followed by definitive anti-tuberculosis treatment; 2 voriconazole and 6 amphotericin-B. The remaining 5 (18%) received antibacterial agents as empirical antibiotic regimen followed by definitive anti-tuberculosis treatment. The median time from chest CT to anti-tuberculosis treatment in the 28 transplant patients with tuberculosis was 7.0 days (IQR 2.0–25.8). Of these 28 patients, 11 (39%) received a initial CT reading reporting tuberculosis as a possible radiologic diagnosis after CT scan, and 10 of these 11 patients received empirical anti-tuberculosis treatment. The median time from CT scan to anti-tuberculosis treatment in the 11 patients in whom possible radiologic diagnosis was tuberculosis was 2.0 days whereas that in the 17 patients in whom possible radiologic diagnosis was not tuberculosis was 17 days ($P = .02$). It is clear that some patients with tuberculosis were misdiagnosed as IPA and received inappropriate antifungal therapy and delayed anti-tuberculosis therapy.

Blind Review

The 2 independent experienced radiologists scored blind 28 tuberculosis and 50 randomly selected IPA cases. The detailed results are shown in Table 2. The sensitivities of radiologist A and B for IPA were 78% and 68%, respectively (poor agreement, kappa value = 0.25), whereas their sensitivities for tuberculosis were 64% and 61%, respectively (excellent agreement, kappa value = 0.77) (Table 2).

CT Features of Pulmonary Tuberculosis and IPA in the Transplant Recipients

We compared the CT findings in the 28 patients with tuberculosis and the 80 patients with IPA (Table 3). Figures 2 and 3 show the typical clinical examples of the CT findings of patients with IPA whereas Figures 4 and 5 show typical examples of IPA-mimicking tuberculosis. Infarct-shaped consolidations,

Table 3. Computed Tomography Findings in Pulmonary tuberculosis and IPA in Transplant Recipients

	TB (n = 28)	IPA (n = 80)	*P* Value
Angioinvasive form			
Macronodule (≥1 cm in diameter)	10 (36)	44 (56)	.07
Single	7 (25)	17 (22)	.70
Multiple	3 (11)	27 (34)	.02
Consolidation, mass shaped	18 (64)	26 (33)	.004
Single	12 (43)	17 (22)	.03
Multiple	6 (21)	9 (11)	.21
Consolidation, infarct shaped	0	22 (28)	.002
Single	0	11 (14)	.06
Multiple	0	11 (14)	.06
Halo sign	0	10 (13)	.06
Airway invasive form			
Clusters of centrilobular nodules (<1 cm)	24 (86)	42 (53)	.002
Tree-in-bud appearance	13 (46)	0	<.001
Consolidation, peribronchial	7 (25)	34 (43)	.10
Ground-glass opacity	13 (46)	48 (60)	.21
Smooth bronchial wall thickening	0	31 (39)	<.001
Necrotizing pneumonia form			
Cavitary lesion	5 (18)	22 (28)	.30
Internal low attenuation	7 (25)	18 (23)	.81
Reverse halo sign	0	1 (1)	>.99
Air bronchogram	8 (29)	34 (43)	.31
Atelectasis	0	8 (10)	.11
Hilar/mediastinal lymphadenopathy	6 (21)	6 (8)	.07
Pleural effusion	16 (57)	43 (54)	.80
Pericardial effusion	6 (21)	10 (13)	.35
Old TB scar	7 (25)	9 (11)	.12
Location of representative lesion			
Right upper lobe	15 (54)	9 (11)	<.001
Right middle lobe	0	9 (11)	.11
Right lower lobe	3 (11)	25 (31)	.03
Left upper lobe	4 (14)	16 (20)	.50
Left lower lobe	3 (11)	15 (19)	.39
Diffuse bilateral infiltrations	2 (7)	6 (8)	>.99

Note: Data are no. (%) of patients, unless otherwise indicated.

Abbreviations: IPA, invasive pulmonary aspergillosis; TB, tuberculosis.

multiple macronodules (Figure 2), and smooth bronchial wall thickenings (Figure 3) were more frequent in IPA, and mass-shaped consolidations (Figure 5) and centrilobular nodules (<10 mm, clustered), especially the tree-in-bud appearance (Figure 4), were more frequent in tuberculosis. In addition, upper lobe dominance was more frequent in tuberculosis than IPA (Figure 5). However, the frequencies of old tuberculosis scars, cavitary lung lesions (Figure 2), internal low attenuation signs, air bronchograms, and pleural or pericardial effusions were similar in tuberculosis and IPA.

DISCUSSION

In this study we found that about two-third of transplant recipients who developed tuberculosis were presented with pulmonary tuberculosis, which yielded a variety of radiologic findings. In addition, we showed that the radiologists had difficulty differentiating pulmonary tuberculosis from IPA in transplant recipients regardless of their experience since the CT findings in about one third of the transplant recipients with pulmonary tuberculosis were very similar to those in the transplant recipients with IPA, whereas the more experienced radiologist tended to accurately diagnose IPA. We thus infer from this study that clinical suspicion and appropriate microbiologic work-up for pulmonary tuberculosis are warranted in transplant recipients who are suspected of having IPA, especially in an intermediate or high-tuberculosis burden country.

Tuberculosis is one of the most important opportunistic infections in solid organ transplant recipients and HCT recipients [1, 16]. The clinical suspicion and early diagnosis of pulmonary tuberculosis relies heavily on imaging modes such as chest CT because the rapid specific diagnostic tests such as the acid-fast bacillus smear and *M. tuberculosis* PCR from respiratory specimens lack sufficient sensitivity [17]. Previous studies have shown that an atypical radiologic pattern may be seen in immunocompromised patients with pulmonary tuberculosis due to altered immunological responses [3]. However, there are limited CT findings in transplant recipient with pulmonary tuberculosis. One study reported the detailed CT findings in 7 HCT recipients who developed tuberculosis; these showed that consolidations (100%), nodules (71%), tree-in-buds (43%), and ground-glass opacities (43%) were frequent [18]. IPA, which is an important opportunistic infection in transplant recipients, also relies heavily on CT for early diagnosis because sputum culture and serum or BAL GM assays have limited sensitivity [9]. In addition, macronodules and consolidations are frequent CT findings in IPA [19]. Indeed, we discovered that about one-third of the transplant recipients with pulmonary tuberculosis were misdiagnosed as IPA and had received inappropriate antifungal treatment. In addition, this study demonstrated that the CT findings in one-third of the transplant recipients with pulmonary tuberculosis were very similar to those in the transplant recipients with IPA. To our knowledge, this is the first study systemically comparing the clinical features and CT findings in transplant recipients with tuberculosis with those in transplant recipients with IPA.

We assume that most adult transplant recipients developed tuberculosis by reactivation due to immunosuppression rather than de novo primary infection [20]. However, here in transplant recipients with probably postprimary tuberculosis, atypical CT manifestations compared with the known postprimary tuberculosis in nonimmunocompromised patients were frequently observed, and some proportion of primary tuberculosis features

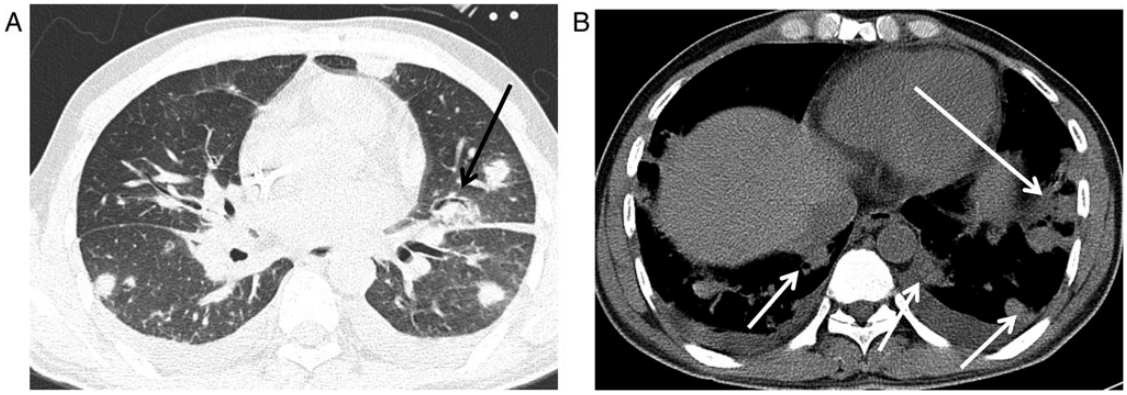

Figure 2. Computed tomography (CT) images obtained in a 45-year-old man with angio-invasive pulmonary aspergillosis and who had received a hematopoietic stem cell transplant 13 months previously. *A*, High resolution CT lung image (1-mm thick) obtained at the level of the lower pulmonary veins. Image shows ill-defined macronodules with halo signs in both lungs. Note the nodule with an air-crescent sign in the left upper lobe (arrow). *B*, Conventional CT mediastinal image (5-mm thick) obtained at the level of the right hemidiaphragm. The image shows bilateral pleural effusion. Note the wedge-shaped consolidations (short arrows) in both lower lobes, and the internal cavities in the lateral basal segment of the left lower lobe (long arrow), which indicates lung infarctions by angioinvasion.

were not uncommon. Most confusing CT findings were combined macronodules with or without cavitation, or pneumonia like consolidation in tuberculosis patients (to radiologsts' stance). Ancillary CT findings separately from the most representative lesions in transplant recipients with tuberculosis were less common multiple macronodules, infarct shaped consolidation, smooth bronchial wall thickening, but more common single mass type consolidation, surrounding- or clustered centrilobular nodules (especially with tree-in-bud appearance), and right upper lobar location, compared with those in transplant patients with IPA. These are important clues for CT diagnosis of tuberculosis rather than IPA.

The GM assay has been widely used in the diagnosis of IPA. Interestingly, 2 (12%) of the 17 patients with pulmonary tuberculosis gave positive results in the serum GM assay. In addition, 1 (14%) of 7 patients with pulmonary tuberculosis yielded positive results in the BAL fluid GM assay. To our knowledge, cross-reactivity of the GM assay with *M. tuberculosis* has not been reported. It is known that tuberculosis can damage the bronchi, and aspergillus can colonize the damaged bronchi [21]. This effect might explain the positive BAL fluid GM assay. In addition, we have shown that about 40% of patients with simple aspergilloma give positive serum GM results [21]. So, it is possible that aspergillus colonizing damaged bronchi release GM into the blood stream. Further studies are needed in this area.

The recent study from the United States showed that the diagnosis of tuberculosis was made at a median time of 11.2 months after transplantation [22]. A landmark review also quotes an average time to diagnosis of tuberculosis

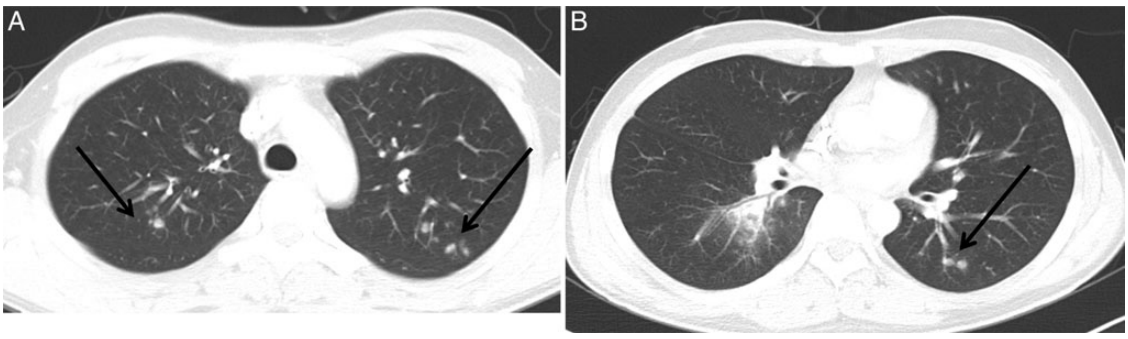

Figure 3. Computed tomography (CT) images obtained in a 29-year-old man with airway-invasive pulmonary aspergillosis who underwent a hematopoietic stem cell transplant 2 months previously. *A* and *B*, Conventional CT lung images (5-mm thick) obtained at the level of the aortic arch and right lower lobar bronchus. The images show ill-defined centrilobular nodules in both upper lobes and left lower lobe (arrows). Note diffuse and smooth thickening of lobar and segmental bronchi of right lower lobe and surrounding halo sign of peribronchial consolidation in right lower lobe.

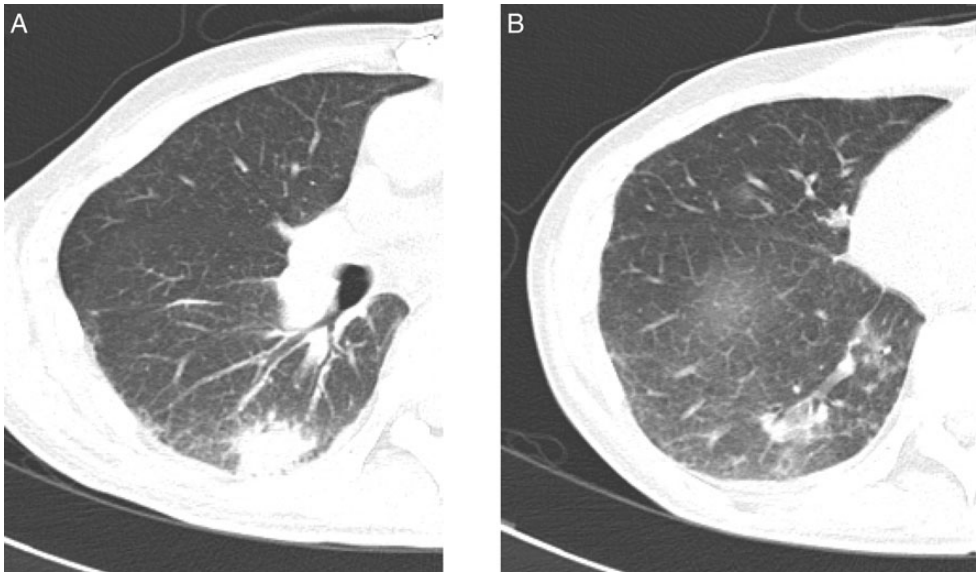

Figure 4. Computed tomography (CT) images obtained in a 48-year-old man with tuberculosis who received heart transplant 10 months previously. *A* and *B*, Conventional CT lung images (5-mm thick) obtained at the level of the bronchus intermedius and right middle lobe. Images show multiple nodular consolidations with surrounding tree-in-bud appearance in right middle lobe and right lower lobe. Note diffuse bronchial wall thickening of superior segment of right lower lobe. He received empirical anti-tuberculous treatment with possible radiologic diagnosis of tuberculosis 1 day after chest CT. Percutaneous core lung biopsy was done, which revealed positive acid-fast bacilli stain and no organism Gomori-Methanamine-Silver & Periodic acid-Schiff stains without granulomatous inflammation. We reported that *M. tuberculosis* complex was cultured in lung biopsy specimen.

post-transplant of 9 months [23]. In contrast, most cases of mold infections such as IPA were reported to occur within the first 90 days after transplantation [24, 25]. However, a recent largest cohort from Spain showed that a median time to tuberculosis onset after transplantation was 6.1 months (range, 0.9–16.6 months) [26]. In addition, a higher proportion of later occurring IPA cases has been reported in recent studies [27, 28]. Our study showed that the time onset for tuberculosis (median 138 days) was longer than that for IPA (median 67 days, $P = .001$). Therefore, the timing of infections after transplantation

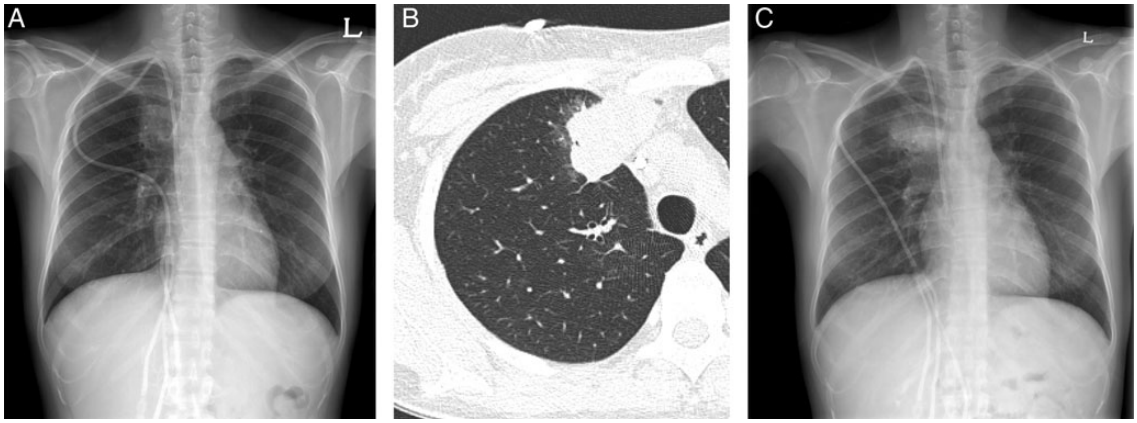

Figure 5. Chest radiographs and computed tomography (CT) image obtained in a 37-year-old woman with tuberculosis who received an allogeneic hematopoietic stem cell transplant 4 months previously. *A*, Chest radiograph showing mass-shaped consolidation in the right upper lobe with positive serum galactomannan (*B*) High resolution CT lung image (1-mm thick) obtained in right upper lobe at the level of the aortic arch. Note the mass with surrounding halo sign. She was readmitted because her symptoms were worsening with aggrevated chest radiograph (*C*) despite of 3-week voriconazole therapy. Percutaneous core lung biopsy was done, which revealed negative acid-fast bacilli stain and Gomori-Methanamine-Silver & Periodic acid-Schiff stains without granulomatous inflammation. At this stage, we reported that *M. tuberculosis* complex was cultured in post-bronchoalveolar lavage sputum specimen that was performed 3 weeks ago.

is helpful for differentiating tuberculosis from IPA. However, this timing is quite overlapping, so other factors should be considered to reach a correct diagnosis.

Our study has several limitations. First some may argue that some patients may been co-infected with tuberculosis and IPA and that this resulted in the IPA-mimicking CT findings in patients with pulmonary tuberculosis. In fact, we excluded one case of tuberculosis and IPA co-infection from the final analysis. Two patients with pulmonary tuberculosis who gave positive GM assays and were included in the final analysis underwent lung biopsies, and these did not reveal any fungal organisms. Second, we only included transplant recipients who developed tuberculosis or IPA after transplantation. Further studies are needed on IPA-mimicking tuberculosis in other immunocompromised patients such as patients infected with human immunodeficiency virus or other immunocompromised hosts. Third, this study was retrospective and was performed in a single large tertiary referral center running active clinical trials and employing the latest treatments for underlying disease. There could therefore be a patient' selection bias. Fourth, the screening and treatment for latent tuberculosis infection (LTBI) in each transplant type in our hospital adopted different policy during the study period except the routine work-up for abnormal chest radiograph. KT and HCT recipients were actively involved in several clinical studies [16, 29, 30] to evaluate the clinical usefulness of tuberculin skin test, QFT-In-Tube, and T-SPOT.*TB*. So, the clinical utility of LTBI screening to differentiate IPA-mimicking tuberculosis from IPA could not be evaluated. So, further studies are needed for the role of LTBI screening results in diagnosing IPA-mimicking tuberculosis. Fifth, the small number of proven IPA cases limits the accurate analysis of the sensitivity of CT findings. In addition, the testing of radiologist's answer does not reflect clinical practice. In real clinical setting, numerous organisms such as pulmonary mucormycosis mimicking IPA instead of just 2 organisms should be differentiated by using given CT findings. Nevertheless, our findings give us valuable information that clinical suspicion and appropriate microbiologic work-up for pulmonary tuberculosis are warranted in transplant recipients who are suspected of IPA, especially in countries with intermediate or high-tuberculosis burdens.

In conclusion, particular CT findings appear to be helpful in differentiating between IPA and tuberculosis in transplant recipients. Nevertheless, the CT findings of about one third of pulmonary tuberculosis cases in transplant recipients were very close to those of IPA. Clinical suspicion and appropriate microbiologic work-up for pulmonary tuberculosis are warranted in transplant recipients who are suspected of having IPA, especially in intermediate or high-tuberculosis burden countries.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Potential conflicts of interest. All authors: No potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Singh N, Paterson DL. *Mycobacterium tuberculosis* infection in solid-organ transplant recipients: impact and implications for management. Clin Infect Dis **1998**; 27:1266–77.
2. Lee KS, Song KS, Lim TH, Kim PN, Kim IY, Lee BH. Adult-onset pulmonary tuberculosis: findings on chest radiographs and CT scans. Am J Roentgenol **1993**; 160:753–8.
3. Van Dyck P, Vanhoenacker FM, Van den Brande P, De Schepper AM. Imaging of pulmonary tuberculosis. Eur Radiol **2003**; 13:1771–85.
4. Singh N, Paterson DL. Aspergillus infections in transplant recipients. Clin Microbiol Rev **2005**; 18:44–69.
5. Lee DG, Kim SH, Kim SY, et al. Evidence-based guidelines for empirical therapy of neutropenic fever in Korea. Korean J Intern Med **2011**; 26:220–52.
6. World Health Organization. Available at: http://www.who.int/tb/country/data/profiles/en/. Accessed 27 October 2014.
7. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European organization for research and treatment of cancer/invasive fungal infections cooperative group and the national institute of allergy and infectious diseases mycoses study group (EORTC/MSG) consensus group. Clin Infect Dis **2008**; 46:1813–21.
8. Park SY, Lee SO, Choi SH, et al. *Aspergillus galactomannan* antigen assay in bronchoalveolar lavage fluid for diagnosis of invasive pulmonary aspergillosis. J Infect **2010**; 61:492–8.
9. Park SY, Lim C, Lee SO, et al. Computed tomography findings in invasive pulmonary aspergillosis in non-neutropenic transplant recipients and neutropenic patients, and their prognostic value. J Infect **2011**; 63:447–56.
10. Lee YJ, Lee SO, Choi SH, et al. Initial voriconazole trough blood levels and clinical outcomes of invasive aspergillosis in patients with hematologic malignancies. Med Mycol **2013**; 51:324–30.
11. Kim SH, Moon SM, Han SH, et al. Epidemiology and clinical outcomes of invasive pulmonary aspergillosis: a nationwide multicenter study in Korea. Infect Chemother **2012**; 44:282–8.
12. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Muller NL, Remy J. Fleischner society: glossary of terms for thoracic imaging. Radiology **2008**; 246:697–722.
13. Logan PM, Primack SL, Miller RR, Muller NL. Invasive aspergillosis of the airways: radiographic, CT, and pathologic findings. Radiology **1994**; 193:383–8.
14. Logan PM, Muller NL. High-resolution computed tomography and pathologic findings in pulmonary aspergillosis: a pictorial essay. Can Assoc Radiol J **1996**; 47:444–52.
15. Collins J, Blankenbaker D, Stern EJ. CT patterns of bronchiolar disease: what is "Tree-in-bud"? Am J Radiol **1998**; 171:365–70.
16. Lee YM, Lee SO, Choi SH, et al. A prospective longitudinal study evaluating the usefulness of the interferon-gamma releasing assay for predicting active tuberculosis in allogeneic hematopoietic stem cell transplant recipients. J Infect **2014**; 69:165–73.

17. Lee YM, Park KH, Kim SM, et al. Diagnostic usefulness of a T-cell-based assay in patients with miliary tuberculosis compared with those with lymph node tuberculosis. Clin Infect Dis **2013**; 56:e26–9.
18. Jung JI, Lee DG, Kim YJ, Yoon HK, Kim CC, Park SH. Pulmonary tuberculosis after hematopoietic stem cell transplantation: radiologic findings. J Thorac Imaging **2009**; 24:10–6.
19. Greene RE, Schlamm HT, Oestmann JW, et al. Imaging findings in acute invasive pulmonary aspergillosis: clinical significance of the halo sign. Clin Infect Dis **2007**; 44:373–9.
20. Aguado JM, Torre-Cisneros J, Fortún J, et al. Tuberculosis in solid-organ transplant recipients: concensus statement of the group for the study of infection in transplant recipients (GESITRA) of the Spanish Society of Infectious Diseases and Clinical Microbiology. Clin Infect Dis **2009**; 48:1276–84.
21. Park SY, Lee SO, Choi SH, et al. Serum and bronchoalveolar lavage fluid galactomannan assays in patients with pulmonary aspergilloma. Clin Infect Dis **2011**; 52:e149–52.
22. Lopez de Castilla D, Schluger NW. Tuberculosis following solid organ transplantation. Transpl Infect Dis **2010**; 12:106–12.
23. Muñoz P, Rodriguez C, Bouza E. *Mycobacterium tuberculosis* infection in recipients of solid organ transplants. Clin Infect Dis **2005**; 40:581–7.
24. Kusne S, Torre-Cisneros J, Manez R, et al. Factors associated with invasive lung aspergillosis and the significance of positive *Aspergillus*culture after liver transplantation. J Infect Dis **1992**; 166:1379–83.
25. Collins LA, Samore MH, Roberts MS, et al. Risk factors for invasive fungal infections complicating orthotopic liver transplantation. J Infect Dis **1994**; 170:644–52.
26. Torre-Cisneros J, Doblas A, Aguado JM, et al. Tuberculosis after solid-organ transplant: incidence, risk factors, and clinical characteristics in the RESITRA (Spanish Network of Infection in Transplantation) cohort. Clin Infect Dis **2009**; 48:1657–65.
27. Gavalda J, Len O, San Juan R, et al. Risk factors of invasive aspergillosis in solid-organ transplant recipients: a case-control study. Clin Infect Dis **2005**; 41:52–9.
28. Singh N, Avery RK, Munoz P, et al. Trends in risk profiles for and mortality associated with invasive aspergillosis among liver transplant recipients. Clin Infect Dis **2003**; 36:46–52.
29. Kim SH, Lee SO, Park JB, et al. A prospective longitudinal study evaluating the usefulness of a T-cell-based assay for latent tuberculosis infection in kidney transplant recipients. Am J Transplant **2011**; 11:1927–35.
30. Kim SH, Lee SO, Kim T, et al. Isoniazid treatment to prevent TB in kidney and pancreas transplant recipients based on an interferon-gamma-releasing assay: an exploratory randomized controlled trial. J Antimicrob Chemother **2015**; 70:1567–72.